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Clinical Proceedings

OF THE CHILDREN'S HOSPITAL

WASHINGTON, D. C.

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(1) Smith, N. J., and Rosello, S.: J. Clin. Nutrition 1:275, 1953. (2) Smith, C. H.: Bull. New York Acad. Med. 30:155, 1954. (3) Niccum, W. L.; Jackson, R. L., and Stearns, G.: A.M.A. Am. J. Dis. Child. 86:553, 1954.

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OF THE CHILDREN'S HOSPITAL

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SARCOIDOSIS

Weekly Case Conference

Sol Katz, M.D.*
Dan Albert, M.D.†
Paul Bender, M.D.‡
Grace H. Guin, M.D.§
Allen E. Marans, M.D.,‖

Sarcoidosis in a colored girl was manifested by uveitis, pulmonary findings and renal lithiasis. These findings and the general nature and treatment of sarcoidosis will be discussed.

CASE REPORT

Dr. Marans:

C. M., an 11 year old colored girl was referred to the Dispensary of the Children's Hospital on March 23, 1954 from Episcopal Eye, Ear & Throat Hospital where she had been seen for the first time the day before. The child had had an inflammation of the left eye for one year and an opacity in that eye for the last three months. Because of the diagnosis of chronic uveitis and the finding of massive cervical adenopathy, a medical work-up was requested.

The past history was non-contributory, revealing no fever, cough, night sweats, weight loss, anorexia or contact with tuberculosis. The family history was likewise negative.

The patient was thin, weighing 47½ pounds, but did not appear ill except for the obvious opacity of the left eye. Her temperature, pulse, respiration and blood pressure were normal and aside from the generalized presence of large, firm, non-tender lymph nodes and the aforementioned eye findings, the physical examination disclosed no abnormalities.

The initial hemogram and urinalysis were within normal limits and a serologic test for syphilis and a heterophile agglutination test were also normal. The total protein was 7.7 gms. per 100 ml. with an A/G ratio of 1.2/1.

Chest x-ray revealed a radiodensity in the lower half of the right chest which had a definite mottled granulomatous appearance with miliary distribution. This was also present to a lesser extent in the left, especially in the hilar regions. X-ray examination of the hands and wrists disclosed no abnormalities. Two tuberculin skin tests (PPD intermediate) were negative.

A left epitrochlear lymph node biopsied on April 18, 1954 was reported to reveal evidence of sarcoidosis. The case was then presented to the Tumor Board which recommended ruling out tuberculosis and then, if indicated, using systemic steroid

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therapy in conjunction with the cortisone and atropine eye drops which had already been started by the Ophthalmology Department.

Three gastric washings grew no acid fast bacilli on culture but the patient was doing well so oral cortisone therapy was deferred. Aside from an episode of pharyngitis, the patient was asymptomatic, although a chest x-ray in June showed some increase in radiodensity over the left chest with the right chest staying about the same.

In August oral cortisone therapy was begun at the suggestion of the Ophthalmology Department because of continued activity in the eye lesion. One week later marked improvement occurred in the eye and one month later considerable resolution in the chest was demonstrable on x-ray. In November x-ray revealed marked fibrotic changes bilaterally with thickening of the interlobar fissure on the right side which represented either fluid or an inflammatory reaction. The eye lesion had become stabilized. Another tuberculin skin test and a histoplasmin skin test were both negative. The hemogram and electrolytes were within normal limits but the corrected sedimentation rate was 41 mm. per hour.

Periumbilical pain, unassociated with abdominal tenderness, nausea or vomiting caused the patient to visit the Dispensary, February 2, 1955 where pyuria was discovered. This persisted despite oral tetracycline therapy. A review of her record at this point disclosed several routine urinalyses in the past which also showed many white blood cells and small amounts of albumin. These had apparently not been associated with symptoms and had evidently been disregarded. An intravenous pyelogram was performed February 10 and revealed three tiny radiodensities in the inferior pole of the right kidney and a larger opacity at the right ureterovesical junction. The right ureter and kidney were enlarged and dilated.

The patient was admitted to the Medical Ward where physical examination disclosed no abnormality other than the opacity of the left eye. Urinalyses revealed pyuria but no cystine crystals and only a normal amount of calcium. Blood studies which included BUN, chlorides, calcium, phosphorus and phosphatase were within normal limits. The total protein was elevated to 8.4 gms. per 100 ml. but the A/G ratio of 1.2/1 persisted. An electrocardiogram was within normal limits as were x-rays of the wrists, hands, feet and long bones. Chest x-ray revealed only fibrosis and another tuberculin skin test was negative.

On the second attempt, a large uric acid stone was removed cystoscopically from the right ureter. The patient recovered uneventfully and was discharged to the Ophthalmology, Urology and Medical Clinics with post-operative x-rays still showing three small right renal opacities.

DISCUSSION

Dr. Guin:

The findings in the lymph node from this child were consistent with the histological criteria for Boeck's sarcoid. The node was replaced by well delineated tubercles composed of epithelioid cells, and a few giant cells scattered throughout. There was a reduction in lymphocytes. There was no caseation. It was a classical illustration of Boeck's sarcoid as we know it from the textbook description.

I think the lead to the diagnosis of this case was pointed to by the ophthalmologists.

Dr. Albert:

This patient was seen at Episcopal Hospital originally. At that time she had an acute exacerbation of a chronic uveitis. This was manifested by the erythema of the left eye, with marked flare in the aqueous humor. With a slit lamp we can detect the increased protein count of the aqueous humor by the observance of the colloids it contains. We can actually do a protein content study merely by seeing how much light is dispersed from the beam going through the aqueous humor. There were many posterior synechiae. By that we mean that the inflammatory processes which have been going on had plastered the iris to the anterior surface of the lens. There was a large iris nodule involving about two-thirds of the inferior portion of the sulcus of the iris. This is described in the procotol as a corneal opacity. Actually it does produce a corneal opacity, because this nodule is so large that it touches the posterior surface of the cornea, producing what we call an anterior synechia. This disturbs the physiology of the cornea and produces a loss of transparency or an opacity. When on her original visit, the cervical and generalized adenopathy was noted, the tentative diagnosis of Boeck's sarcoid was made and she was referred to the out-patient department here. Uveitides are an ophthalmological headache. It is quite unusual that we are able to change a tentative diagnosis into a final diagnosis, as is done in the case here, following biopsy. However, we know that uveal tract inflammation may destroy the anatomy of the eye, and a little bit of disturbance here will disturb the function of the eye, so it is very important that we block any inflammatory reaction that we can in order to maintain function of the eye. This was attempted by using local cortisone, and although there was a questionable improvement, synechiae in the aqueous humor persisted, and it was suggested that the girl transfer to Children's Hospital so that she might be treated with systemic cortisone. As the protocol describes, the response to this treatment was rather dramatic, and although she has never been entirely free of signs of infection, the eye has been going along without an increase in destruction. The right eye has never been involved. This is not the general rule; usually sarcoidosis is a bilateral disease and although it is usually described as a benign disease in the eye, it is not. The prognosis for vision is very poor. In this section where we see so many colored people in the clinics, a big percentage of blindness is due, we believe, to Boeck's sarcoid. So it behooves us to treat it the best we can and take the chance of the complications as have arisen from the therapy in this case.

I believe the child looks today exactly the way she did at Episcopal Hospital a year ago.

Dr. Bender:

Referring back to the x-ray with the right hydro-ureter and hydronephrosis, it is obvious that the stone near the uretero-vesical junction is impacted in the ureter. However, even as such, it was well worth it to try to remove the stone without an open operation. On the first attempt, we were unsuccessful and could not pass a Levant basket beyond the stone; this is a nylon basket containing no metal. Next we tried #3 French ureteral catheters, and again we could not get beyond the stone. After about one hour of manipulations we inserted three catheters up the right ureteral orifice to the stone and left them indwelling for one day. The catheters were then removed and the following day a small fragment of stone came out spontaneously. Five days after the initial attempt we had no difficulty passing a Levant basket and a loop catheter beyond the stone and were successful in removing it. As far as the other stones in the right kidney are concerned the chances are very good that they will pass spontaneously, because they are smaller than the one that has already been removed. There are definitely three stones in the right kidney, and probably a fourth behind the right twelfth rib that does not show too clearly.

There are several factors to explain the formation of stones in children or in someone with sarcoidosis. First of all, the incidence of stones in children is not great. In the kidney it is less than 1 per cent. In the bladder, they average about 1.6 per cent of all urinary tract calculi. Colored people have a lower incidence than white; females less than males.

We do not know whether the stones were formed before the onset of cortisone therapy or after, as no x-rays were taken until after several months of cortisone therapy. It is known that in cases of stress or in patients receiving ACTH or cortisone therapy there is an increased excretion of uric acid in the urine. This naturally predisposes to urinary tract calculi. Uric acid calculi are the most common in children. Other factors that can produce multiple calculi are infections, particularly with urea splitting organisms, stasis, metabolic disturbances which can also include Cushing's disease and hyperparathyroidism; in older individuals, menopausal osteoporosis; and excessive vitamin D intake, high calcium intake, and recumbency, particularly in paraplegics and orthopedic cases. There are various areas in the world where stones are more prevalent, especially outside of the United States in places where the diet is deficient and there is an inadequate vitamin nutrition. This child is also quite malnourished, and perhaps has had some vitamin deficiency. The more frequent type of stones in children is a little different than in adults. This is the predominant composition of urinary calculi in children: uric acid heads the list, then oxalates, phosphates, carbonates, cystine and xanthine. In the adult calcium phosphate and calcium oxalate stones are more common.

Most of the great stone areas are in China, Arabia, the Volga Basin, and in India. You will notice that there are a few places in the United States, mainly in Florida, California and a small section in the midwest where stones are prevalent. The Southern California and Florida regions are attributed to dehydration and high phosphorus in the diet, mainly from citrus fruits.

X-rays on this case show the stones to be quite dense, at least three of them; and two of them in the kidney are of less density. From the x-ray evidence you would believe that they are calcium phosphate or oxalate, and we are much surprised to find that they are uric acid which are considered non-radiopaque or nearly so. If this stone had been a calcium phosphate one it could also be explained on the basis of cortisone therapy, or even on the basis of sarcoidosis. Between 20 and 45 per cent of all patients with sarcoidosis will have a hypercalcemia and a hypercalcinuria. Phosphorus in these cases remains normal, as does the alkaline phosphatase. The calcium that is deposited in the kidneys from this hypercalcemia and hypercalcinuria may take two forms. It may take the form of hypercalcinosis with precipitation of calcium phosphate within the collecting tubules, or it may take the form of a calculus in a kidney as we have here, with eventual progressive destruction of the parenchyma.

As for treatment there are cases on record where patients with sarcoidosis have been treated with cortisone and the hypercalcemia has returned to normal. After several weeks of therapy and the discontinuation of cortisone, hypercalcemia did not return until after 6 to 8 months. The long range prognosis on this child as far as urinary tract calculi are concerned centers around the chemical composition of the stones. Assuming that there is no calcium phosphate in this stone and that it is composed of pure uric acid, even though the x-rays suggest that there is some calcium present, this child should be alkalinized 24 hours a day. The best compound for alkalinization is sodium citrate; one teaspoonful at least 4 times a day. She should have a low uric acid intake, adequate vitamins and a urinary output of at least 1500 cc. This should be measured, because if a child has a 1500 cc. urinary output in the winter she may not have it in the summer. Naturally she should be re-examined about every 3 months with x-rays to see if these stones will enlarge. We hope that she will pass them spontaneously.

Dr. Katz:

This patient certainly presents a very interesting manifestation of sarcoidosis. I was interested in knowing whether there were any skin lesions of even the remotest suspicious kind. I think that is important because too often one waits for skin lesions before a diagnosis of sarcoidosis is made. Now that all of us are becoming more tuned to the diagnosis we do not wait

for skin lesions. In our series only about 10 per cent of the patients have skin lesions. The systemic manifestations therefore are the ones that we should look for in this condition. Ocular manifestations I think we see a little more frequently in the younger people than we do in the older age groups. Most of the people under the age of 15 whom we have had with sarcoidosis have shown eye manifestations. The eye manifestations may vary widely from mere enlargement of the lacrimal glands to extensive involvement of the uveal tract or iris. Out and out blindness may occur.

I think we overlook too often an examination of the lacrimal glands in colored patients. That is not a part of a routine examination certainly, yet it is often rewarding, and I think we also should look at the lacrimal glands of colored patients to get an idea of what the normal lacrimal gland looks like. The colored patient usually has lacrimal glands which are considerably larger than what we are accustomed to seeing in a white patient. I would suggest that we make that a part of the examination and we will be rewarded, because in sarcoidosis the lacrimal glands are not infrequently enlarged, and little white nodules may be seen on the surface which give a very valuable lead. I notice that Dr. Albert mentioned the fact that there was a rather large iris nodule present in this child and I wonder if you could tell us, Dr. Albert, anything about the vascularity in the region of that nodule.

Dr. Albert:

It was very apparent when first seen that this was quite a vascular nodule. In fact there was a large vessel coursing from posterior to anterior across the surface, so that it gave the iris a rather fleshy appearance, which is unusual as compared to those which we consider to be typical granulomatous nodules.

Dr. Katz:

I am glad you mentioned that because some men have felt that the iris nodules are distinctly different in sarcoidosis, in that they are as vascular as you have just described, while in tuberculosis very commonly the vascularity is around a nodule rather than with the vessels coursing through it as was described here. Another thing which the ophthalmologists often are able to tell us is that there are "mutton-fat" precipitates in the posterior area of the cornea. Now those are not pathognomonic of sarcoidosis, because they are also seen in tuberculosis and syphilis. We have to look, I think, not infrequently to the ophthalmologist for a clue to this disease. I was distressed at Dr. Albert's statements that usually the diagnosis of sarcoid uveitis is a presumptive one. Perhaps it should not always be that way. Sarcoidosis should be diagnosed in close to 100 per cent of the cases, unless

perhaps only the eye is involved which is rather unusual. The patient was thin, and I have yet to see an obese child who has sarcoidosis. Reasons for that, I suppose, are many.

The x-rays were of some interest to me. In the very first film, one can see a rather striking increase in the right paratracheal node. The transverse fissure is rather dense with changes described at both bases. It is so often stated that pleurisy does not occur in sarcoidosis and that pleural effusion is unheard of. Since we have been doing pleural biopsies, in the diagnosis of pleural diseases of various kinds, we have seen a number of patients with sarcoidosis involving the pleura and two with pleurisy with effusion. I think it is a point that pleurisy with effusion or pleural involvement is rarer in sarcoidosis than in tuberculosis, but it does not exclude the diagnosis when it is present. The x-ray manifestations are variable; enlargement of the hilar lymph nodes is very common, and I would call your attention to the fact that commonly the hilar lymph node involvement is symmetrical. The right hilar group is almost a mirror image of the left hilar group. The paratracheal nodes are involved very commonly but there is nothing significant diagnostically about the involvement of the right paratracheal group, because, as you know, normally there are more nodes in the right paratracheal or the azygos area than in the left paratracheal area. One often sees linear striations extending from the inferior margins or inferior poles of these large "potato nodes" towards the diaphragm, particularly the inner thirds. We usually consider involvement of the hilar nodes like this a manifestation of early sarcoidosis. In addition to the hilar node involvement one frequently sees a nodular or miliary pattern. Often the nodules are of varying size, not always as uniform as one sees in miliary tuberculosis, but they may be indistinguishable from miliary tuberculosis. Again the miliary involvement is symmetrical. This also can be considered as a manifestation of early sarcoidosis. Another thing one sees in early sarcoidosis is a patchy consolidation like a bronchial pneumonia and often very symmetrical. These features, namely the lymph nodes by themselves, or the miliary nodules, or the patchy bronchial pneumonia variety are considered samples of early x-ray findings. They may have been present for a year, but it is still early as compared with the second large group of x-ray findings, namely, a reticulated pattern in which one sees scattered throughout the lung fields rather marked linear striations extending from the lymph nodes very commonly. This reticulated pattern is a much later manifestation and is more often associated with respiratory symptoms than the early group which I outlined. The third variety, which is seen very infrequently in children and very frequently in adults, is the fibrotic emphysematous stage in which the patient has a chest which looks very much like the patient with extensive emphysema and fibrosis. This group is the most symptomatic one. We do

not look upon sarcoidosis as a benign disease in the patients who present this kind of x-ray manifestation, because they are severely incapacitated, and their pulmonary function is markedly abnormal.

The next thing that caught my eye was this large left epitrochlear lymph node biopsy. In sarcoidosis even a small epitrochlear node may be significant. We urge always that if you feel for an epitrochlear node, even though you are not convinced that it is globular, and it seems like a flat, normal eiptrochlear node, take it out as a simple procedure because so often you will be rewarded by a pathologic node. Dr. Guin told us that the pathological findings were consistent with sarcoidosis or showed the sarcoid structure. I am glad she put it that way, because I do not think we should look to the pathologist to make a diagnosis of sarcoidosis for us. The most they can tell us is that this biopsy material shows a sarcoid structure. It may be that it is histoplasmosis or brucellosis, or one of a wide variety of occult diseases which can give a perfectly typical sarcoid structure; often a misdiagnosis is made because the pathologist says this is sarcoidosis. If a fungus stain is not done, we may miss a diagnosis of histoplasmosis, because the pathology is so typical of sarcoidosis. Rather one should correlate the pathologist's finding of a sarcoid structure with the clinical picture, which was done here.

It was striking to note here that there was a marked improvement following cortisone. We therefore have to attribute the change to cortisone because in sarcoidosis one does not see dramatic change occurring quickly or spontaneously. When in the course of a few weeks or a month one sees a dramatic change, whether it be in x-ray or the size of a lymph node or the improvement in the eye lesion, one can say this was due to the therapy and was not a spontaneous remission. I am glad to see a histoplasmin skin test was done too, because the picture of sarcoidosis may be indistinguishable from histoplasmosis. The Armed Forces Institute learned this the hard way. Not long ago they had three patients who were carried on their files as classical examples of sarcoidosis, all three of whom subsequently died of adrenal insufficiency and had widespread histoplasmosis identifiable when the proper stains were done, even on the material they had called sarcoidosis. So I think that in certain areas (Tennessee Valley Area, Ohio Valley Area, Missouri Valley Area) when one sees sarcoidosis it would be well to look too for the possibility of histoplasmosis. We thought that perhaps there might be some value to screening our patients for histoplasmosis because nobody knows what causes sarcoidosis, and possibly more cases are due to histoplasmosis than we realize. In doing skin tests and serologic studies on our group of patients with sarcoidosis we found no increased incidence of histoplasmosis over the patients that did not have sarcoidosis.

The kidney manifestations are certainly very fascinating in this disease.

Pathologically, at least at autopsy, one finds sarcoidal involvement of the kidneys in about 20 per cent of the patients. I mean sarcoidal involvement as a pathologic finding, not as one of clinical significance. However, sarcoidosis may involve the kidney extensively and cause renal insufficiency. I am sure most of you read a report not long ago in the *New England Journal of Medicine* of the first documented case of sarcoidosis of the kidney to the point of uremia. However, this syndrome as we see it in the patient here today is not terribly uncommon. We make it a routine to do flat plates of the abdomen in patients who have sarcoidosis, looking for nephrocalcinosis or nephrolithiasis. The soft tissue calcifications may be elsewhere than in the kidney and may involve the periarticular structures, but they are readily found in the kidney when present, and as Dr. Bender indicated, usually are of calcium content. It surprises me for stones as dense as this to be uric acid stones, since all of us have been taught that these are the stones that have about the least radiodensity. The stones in the kidney themselves are even denser and more sharply defined and look more than ever like calcium phosphate stones.

No one quite knows why this hypercalcemia occurs in sarcoidosis. In practically all the cases of sarcoidosis with nephrocalcinosis or nephrolithiasis that I know of, there are some interesting manifestations in addition to this. We find that they will have premature arteriosclerosis not uncommonly. Their gastric rugae may be very hypertrophic and may even be seen on a flat film of the abdomen, but whether this represents actual sarcoid involvement of the gastric mucosa has not been determined. Films of the pelvis will disclose calcification quite prematurely in the absence of diabetes in these patients.

As for the phosphatase, I would like to differ a little bit with Dr. Bender and point out that the phosphatase is elevated rather frequently in sarcoidosis, unrelated to the bone metabolism or the hypercalcemia but rather as a common manifestation of liver involvement. The liver is involved in 75 per cent of patients with sarcoidosis, whether or not the liver can be felt and whether or not there are abnormal liver function tests. So we look to liver biopsy as a very fruitful technique for making a tissue diagnosis in sarcoidosis. The elevated phosphatase is a manifestation of the granulomatous process in the liver, just as it may be in tuberculosis of the liver. The phosphorus, as was indicated, was normal and is of some differential aid in distinguishing sarcoidosis from hyperparathyroidism which can also cause this syndrome.

I have not mentioned that this patient had normal hand films and I think we should expect them to be normal. In 90 percent of the patients with sarcoidosis who have bone involvement you can almost predict involvement of bones of the hands or feet because the fingers are broadened or deformed,

or the tips are widened, or there is some abnormality in the shape. Bone involvement which occurs in only about 10 percent of the cases may be of two kinds, either the punched out areas which are not pathognomonic, or the trabeculated reticulated pattern which is fairly pathognomonic except perhaps for leprosy. The bone involvement is usually in the bones of the hands and the feet, and occasionally in the carpal bones, long bones, and nasal bones.

Other organs have been involved in this disease: the heart is not infrequently involved even to the point of heart failure; the spleen is involved very commonly, and lymph nodes of course almost universally.

I would be reluctant to make a diagnosis of sarcoidosis if there were not enlarged lymph nodes someplace, either in the mediastinum or periphery. We find that 75 percent have peripheral nodes, 85 percent have mediastinal nodes, and 100 percent have one or the other or both. In other words, lymph-node involvement is present someplace in virtually all cases of sarcoidosis, and the lymph nodes may be tiny or they may be massive.

We cannot expect the laboratory to help us completely. The laboratory can tell us something about the white blood count which is usually perfectly normal, or the red blood count which is normal except in those patients who have hypersplenism. The calcium may be somewhat increased, the phosphatase somewhat increased, and the globulin of course elevated, but there is nothing specific about the laboratory findings, so we have to look to biopsy material. When there is an obvious site for biopsy such as a skin lesion or a palpable node, of course there is no question, but when there is no obvious site, then one has to look to other techniques, and the scalene lymph node has given us a very fruitful technique in diagnosis. About two-thirds of the patients with sarcoidosis in whom there is demonstrable involvement of the mediastinal nodes will show an involved scalene node. Dr. Harkens has gone a little further than the scalene node and has used a laryngoscope or a thoracoscope through the scalene approach down into the cervical mediastinal region as far as the carina to biopsy a node and we can expect with that technique, that involved nodes will be found more frequently. Lung biopsy should be used as a very valuable technique and is not a terrible procedure at all. In adults it can even be done under local, although most surgeons, in this area at least, prefer general anesthesia. It is not a difficult procedure and there is little morbidity and zero mortality. Most patients can be discharged one or two days after the procedure is done.

The prognosis in sarcoidosis is said to be good and the mortality is said to be low, but I am not so sure of that. It is also said to be an asymptomatic illness but symptoms are common in sarcoidosis and death is not infrequent, especially in adults where we find the lung involvement to be great and pulmonary insufficiency, cor pulmonale, and repeated episodes of pneu-

monia to be so common. I do not want to paint a real black picture because most patients with sarcoidosis will be alive for five or ten years. Dr. David Carr has summarized cases at the Mayo Clinic and finds that in about 200 cases 93 percent are alive after five years and 80 percent are alive after 10 years. The prognosis even in a rather selected series is good. We find our mortality higher than they have found, but we have had many more colored patients in our series than they had. This matter of race distribution seems rather interesting. It does seem more common in the colored; 17 to 1 roughly. As for the geographical location, we have tried to confirm the findings of Drs. Max Michael and Beeson, who did a nice epidemiologic study analyzing the origin of the patients with sarcoidosis whose diseases were picked up during the war. These two men found that the bulk of their patients came from the southeastern part of the United States, and especially the rural areas of that section. We have not found that to be so, although we are in the southeast and most of our patients come from this part of the country. The Mayo Clinic recently published their epidemiologic study and found that there was no difference in the distribution of their patients with sarcoidosis from their general census of patients. However, as soon as Dr. Michael and the United States Public Health Service came forth with an epidemiological study everybody got to work to see what there might be in the southeastern part of the United States that made sarcoidosis a disease found in the rural area and not ten miles away in a city in the same vicinity. The geologists found that there was a soil, a Norfolk Rustin soil, whose distribution pinpointed the distribution of sarcoidosis. Others came along and asserted that it was something else. At the moment, nothing has come of this and sarcoidosis is still a disease of unknown etiology.

As therapy, I think we had very little to offer the patient until cortisone came along. Calciferol, vitamin D_2, tuberculin, carbon dioxide snow, gold and x-ray therapy really did not do a great deal. As for the indications for the use of cortisone, no one is quite sure, and I think we would all agree that in the patients without symptoms of sarcoidosis, especially the patients with enlarged lymph nodes or a patchy pulmonary infiltrate, that nothing should be done. On the other hand, if there is pulmonary insufficiency, cortisone should be used. If there is involvement of significant organs other than the skin or lymph nodes, such as the eye, the heart or the liver, there would be a strong indication. Most people feel that this syndrome of nephrocalcinosis is an indication for cortisone, using the low calcium diet and the other things that Dr. Bender suggested while continuing cortisone. The question might be asked, "Why not give cortisone to patients who have a miliary pattern; why wait until they go on to pulmonary insufficiency?" It has been demonstrated that very frequently giving cortisone to these patients will result not in complete resolution of these granulomatous

nodules, but in a rather heavy deposition of fibrous tissue, so there may be an increase in their pulmonary insufficiency rather than a decrease. In an asymptomatic individual it would not seem worthwhile taking chances on creating a respiratory cripple.

As for the incidence of tuberculosis in sarcoidosis, I think the consensus is now that there is probably not any increased incidence of tuberculosis in sarcoidosis over the general population. Good studies have indicated that to be so. I think one of the reasons we saw tuberculosis in sarcoidosis is that the diagnosis was not made and these patients were sent to tuberculosis sanitoriums very commonly. The way we got interested in sarcoidosis was this: we had a patient who was transferred to the D. C. General Hospital from Glenn Dale where she had been for three years. She wanted to transfer because her family found it difficult to travel that great distance. She was admitted with stage 3 sarcoidosis with extensive involvement of the lungs, emphysematous bullae, and cor pulmonale, but she had a negative tuberculin test even though she had been at Glenn Dale for three years. That seemed a little inconsistent with the large liver, the large spleen, and large lymph nodes, so a node was biopsied and showed sarcoidosis. It is not unusual to find patients with sarcoidosis in tuberculosis sanitoriums, and I expect therefore, they should get more tuberculosis than those who are outside the sanitorium. I think from surveys done since 1944, that the incidence of tuberculosis is no greater in sarcoidosis than in the general population. That gives those people who worry about using cortisone in these patients some comfort, because, as you know, there has been some objection to using cortisone in patients who have tuberculosis. I am not sure that that is justified. Dr. Lovelock feels that patients who are given cortisone for sarcoidosis should have concomitant anti-tuberculous therapy. I do not think many people agree with him, however.

Question: Is sarcoidosis frequently seen involving only an eye?

Dr. Katz:

The manifestations may be related only to one organ, but it is most unusual to have sarcoidosis involving only the eye. Lymph nodes are involved practically always and liver is involved frequently. We have patients who have perfectly normal livers in all respects; normal liver function test, normal phosphatase, normal sized liver, and the biopsy shows the typical granulomatous epithelioid reaction of sarcoidosis. I think it would be most unusual to have an organ like the eye involved alone, which is why I say that I think the diagnosis should be made frequently. I think perhaps as far as the ophthalmologists are concerned, that they do see a group of patients who have chronic uveitis and that is where it stays. The diagnosis

is chronic uveitis, cause undetermined. I personally feel that those are not sarcoidosis unless we can find organ involvement elsewhere.

Question: X-ray of the chest of the patient last year was considerably clearer than the one taken a week or two weeks ago. The child has been kept on cortisone right on through, and in spite of that there seems to be some increase in the x-ray lesions. How would you explain that?

Dr. Katz:

One sees this happening in cortisone therapy. We will see patients whose skin lesions improve while his lymph nodes are getting larger or staying the same, or those whose lung lesions improve while skin lesions are not touched. There is a disparity in the response. I think that the more fixed the pulmonary change, the less one should expect, and since these patients are subject to acute infections at times, one sees the altered x-rays attributed not to an exacerbation of their sarcoid lesions but to an infection. If this x-ray change persists I think it would be more likely an extension of the sarcoid process, and thus an indication for continued cortisone therapy. Here is a disease which has a course characterized by remissions and exacerbations, so I think giving a week of cortisone and then stopping is rather useless. We keep cortisone therapy going for rarely less than two months and in most cases longer than that.

Question: Have you anything that would completely cure the patients with advanced sarcoidosis?

Dr. Katz:

No. I think once a patient reaches this stage 3 of fibrosis and emphysema he faces the poor prognosis that goes with that terrific lung process, so we direct our attention towards trying to improve ventilation, lessen the bronchospasm, treat the infection and the cor pulmonale, but we do little for the basic disease once fibrosis has occurred. We cannot, like the plastic surgeons, cut out a scar on a lung very readily.

PIERRE ROBIN SYNDROME

Donald R. Pohl, M.D.*

Pierre Robin of Paris, France, in 1926 first described a condition of hypoplasia of the mandible, cleft palate, and glossoptosis with accompanying inspiratory retraction of the sternum, cyanosis and malnutrition[1]. This syndrome which now bears his name has also been called the Dodd syndrome. Cursory review of the literature has uncovered approximately 39

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reported cases: 12 by Douglas[2], 27 by thirty-eight surgeons in a survey[2]. There are 9 in the files of Dr. Robert Moran[3]. There are undoubtedly many more unreported cases of the syndrome.

This syndrome becomes clinically significant due to the obstructive dyspnea caused by the tongue falling posteriorly and downward into the pharynx. Douglas has termed this "linguo-epiglottic obstruction"[4]. These infants if properly taken care of, as a rule, do well. There are, however, several points in care that need to be emphasized.

This paper presents a case of Pierre Robin syndrome which has been recently observed at Children's Hospital.

CASE REPORT

Baby H., a colored girl was born at another hospital on July 17, 1956. The patient was transferred to Children's Hospital two and one-half hours after birth with a diagnosis of cleft palate and possible congenital atresia or obstruction below the larynx. The mother was Gravida 6, but this was her first full term delivery. Previous pregnancies had resulted in four abortions at three months gestation and one at five months gestation. During the present pregnancy she simultaneously had mumps and chicken pox during the third and fourth month of pregnancy. Birth of this infant

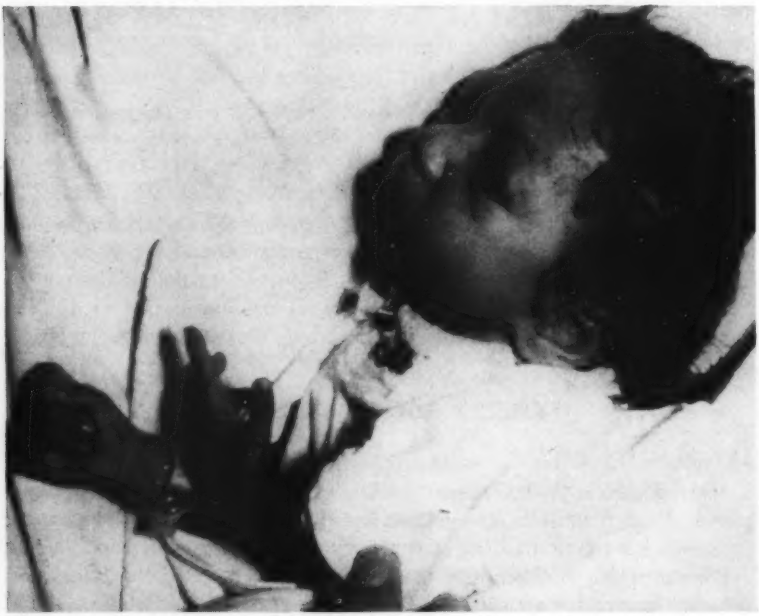

FIG. 1. The characteristic hypoplasia of the mandible seen in the Pierre Robin syndrome.

was uneventful but she did not cry for ten minutes after delivery. Her first cry was shrill in nature but later became that of a normal newborn. She was cyanotic for two to three minutes after birth but became pink after administration of positive pressure oxygen. This cyanosis was accompanied by marked rib retractions at first but later subsided. When a catheter was passed through the nose, an obstruction was encountered. Examination revealed this apparent obstruction to be the tongue which was adherent to the roof of the mouth. When the tongue was pulled down and forward, a cleft palate was revealed.

Examination of the infant at this hospital revealed a well developed negro girl weighing 5 pounds, 11 ounces. She appeared to be having respiratory difficulty despite the presence of an oral airway. The cleft palate involved three-fourths of the hard palate and the entire soft palate. The tongue was arched backwards into the pharynx. Her chin was receded markedly (Figure 1). As long as the tongue was prevented from obstructing the pharynx, respirations were fairly regular and the lung fields appeared to be well aerated.

Four hours later while the patient was being examined, the tongue was observed to have fallen back into the pharynx. Respirations ceased momentarily and the heart rate dropped to 40 per minute. When the tongue was pulled forward with forceps respiration became normal. However, since the child still did not breathe without difficulty a tracheotomy was performed under local anesthesia.

After the tracheotomy, the infant was placed in an incubator with additional oxygen. She continued to breathe at the rate of 80 per minute, however, and cerebral damage was suspected. Lumbar puncture revealed normal spinal fluid.

Over the next two week period the infant was noted to be having increasing episodes of cyanosis and respiratory failure. These always responded well and rapidly to artificial respiration. The tracheotomy tube was patent during these episodes.

Initially, feeding was by gavage. The child did well, gaining weight very slowly. Later she was fed by nipple which she took fairly well. Supplementary formula was given by gavage. She had no more episodes of cyanosis but still had periods of irregular breathing. By use of thickened feedings and patience over the next 20 days the child was gradually weaned off gavage feedings and took her entire daily food requirement by nipple.

An attempt at occluding the tracheotomy tube rapidly brought on respiratory distress. On August 22, 1956 laryngoscopy was performed. On the basis of this examination it was felt that she had a laryngomalacia. The vocal cords were not visualized. An electroencephalogram done on August 23, 1956 was normal.

The infant took her formula satisfactorily and appeared to be doing well, but on the 67th hospital day again had several episodes of cyanosis. On the 69th day she was found dead in her crib after being left alone for a few minutes.

Postmortem examination revealed a polyp in the trachea just above the tracheotomy opening. The brain showed no gross abnormal changes.

DISCUSSION

This patient was brought to us several hours after birth. Rather than having the Douglas procedure[4], which is suturing the tongue over the lower gum to the mucous membrane in the sulcus below the free border of the lower lip, this child had a tracheotomy because it was felt that with the tongue pulled out she was still in danger of respiratory obstruction. This was later proven at laryngoscopy where the laryngomalacia was discovered.

The tongue in this syndrome falls backward and downward into the pharynx and over the epiglottis giving rise to a ball valve type of obstruction. Normally the tongue is held forward mainly by the genioglossi muscles (attached to the mental spines at the symphysis of the mandible) and the frenulum linguae. In micrognathia the receded position of the mandible allows the tongue little if any support. As the mandible grows, (and in 9 to 12 months most chins are growing to normal size) the tongue begins to get increasing support. With the Douglas procedure a minimum of six weeks and an average of two months is needed until the tongue has enough support so that it may be released with safety.

Pruzansky[5] with the aid of roentgenograms has shown that the mandible, even without stimulation of any kind, will grow. This growth is sufficient to overcome the extreme recession of the chin observed at birth. Since mandibular growth continues until late adolescence, it is possible to hope for and to expect a pleasing profile in adulthood. The cleft palate is repaired surgically, preferably at the age of 18 months to 3 years.

Feeding is probably one of the bigger problems with these infants. Davis and Dunn[6] have designed a lip guard which they feel aids greatly in the exercise of the muscles and consequent development of the mandible. This apparatus consists of a cap sleeve with a solid perpendicular rod and lip guard fastened to an ordinary nursing bottle by a set screw. The lip guard rests against the upper lip and forces the infant to protrude his lower lip and jaw, thus gradually adjusting to a position further and further ahead of the rubber nipple. Since we did not have this apparatus, early feeding was extremely difficult. With increasing age, however, her ability to use an ordinary nipple had progressively improved.

It is felt by Kitlowski[7] that "in many of these cases there are complicating factors in the skull which keep the cyanosis persisting, even though the apparent obstruction is relieved." This was the feeling in our patient since with these periods of cyanosis, the tracheotomy tube was apparently clear. However, the electroencephalogram was normal and except for the episodes of cyanosis there was no other evidence of brain involvement, even on post-mortem examination

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JEJUNAL ATRESIA WITH ASSOCIATED CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

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We have recently encountered a case of jejunal atresia with associated congenital hypertrophic pyloric stenosis. Because of the rarity of this combination in medical literature, we feel this case deserves special report.

CASE REPORT

Baby P., a white girl, was born at Columbia Hospital on June 16, 1956 and transferred to Children's Hospital at 8 hours of age because of abdominal distension noted at birth. Her birth weight was 7 pounds 13 ounces and insofar as is known, the gestation and delivery were both normal.

Physical examination on admission revealed a well developed and nourished newborn in no apparent distress, with no evidence of cyanosis but with obvious abdominal distension and visible loops of bowel beneath the skin. These were more pronounced on the left side of the abdomen. Her rectal temperature was 99 degrees Fahrenheit; respirations were 40 per minute and the pulse was 150 per minute. The face and neck showed some small abraded areas. The abdomen was markedly distended with several veins visible on the anterior abdominal wall, and on palpation a "doughy" sensation with "nodular masses" was felt. The liver was palpable 4 centimeters below the right costal margin, and the spleen 4 centimeters below the left costal margin. Normal peristalsis was heard. The anus was patent and a rubber catheter was passed some 5 centimeters into the rectum without difficulty. No meconium was noted. The remainder of the physical examination was within normal limits. Her admission blood count was 16,500 leukocytes with a differential of 73 percent segmented and band forms, 21 percent lymphocytes, 1 percent young forms, 3 percent monocytes, 1 percent eosinophiles, and 1 percent basophiles. The hemoglobin was 22 grams and the hematocrit was 68 percent. Admission urinalysis showed an acid urine with 300 milligrams percent albumin and a positive test for bilirubin. There were 10–20 white cells per high power field, 0–1 hyaline casts and 1–3 granular casts with an occasional pus cast.

Roentgenograms taken on admission were reported as showing "a few loops of distended small bowel" with "an absence of gas in the rectum. The appearance is that of an organic intestinal obstruction, probably in the ileum and most likely representing a meconium ileus" (Figure 1).

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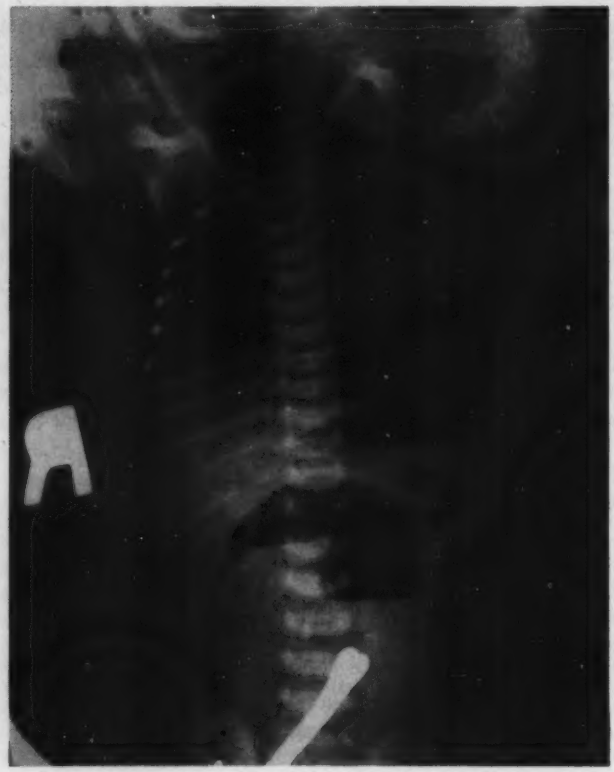

FIG. 1. Upright film of abdomen obtained immediately after admission. Note the "bubbly" gas pattern throughout the intestinal tract suggestive of meconium ileus. There are a few loops of distended small bowel and an absence of gas in the large bowel and rectum, indicative of an organic intestinal obstruction probably located in the terminal ileum.

At twelve hours of age exploratory laparotomy was performed. The operative findings consisted of:

a) Adhesions of the entire small bowel with flecks of meconium present in the abdominal cavity;

b) A dilated jejunum ending in a blind pouch and filled with a dark fluid.

The proximal stoma was resected for a distance of 18 inches, and the distal stoma resected approximately 2 inches. A two layer side to side jejuno-ileostomy was then performed.

Her immediate postoperative condition was good. Antibiotics in the form of penicillin and streptomycin were administered and Wangensteen drainage instituted. Two repeat roentgenograms taken on June 19 and June 22, due to regurgitation of

bile, revealed, respectively "absence of gas in the distal portion of the colon is reliable evidence of obstruction." "Obstruction believed still to be present." Her weight at the end of the first postoperative week was 6 pounds, and 2 ounces.

Feedings of Olac® formula (1:3) were begun, one ounce every two hours. This was gradually increased to a 1:2 ratio with additional calories in the form of Dextri-Maltose.® Supplemental fluids were given by hypodermoclysis. She continued to vomit but gradually began to retain fluids.

Two weeks after operation, roentgenograms were again repeated due to the continued intermittent vomiting and reported: "no gas is visualized in the small intestine or colon. An intestinal obstruction high up cannot be ruled out."

On July 5 the patient was re-explored and a hypertrophic pyloric stenosis was found to be present. This was corrected by the Fredet-Ramstedt procedure. Postoperatively the patient was transfused with 50 milliliters of whole blood, and oral feedings of 5 percent Dextrose in water begun. Penicillin and streptomycin were given in large doses and the child began to pass stools with regularity. Her weight was now 5 pounds, and 8 ounces.

Postoperatively, her course was something less than satisfactory. She continued to regurgitate some feedings and "milk stools" were passed. By the second week she began having 10 to 12 watery stools daily and needed supplementary clyses for maintenence of fluid balance. She was then transferred to the diarrhea ward and given Hi-Pro® 1:3 and Lytren® by mouth. The strength of the formula was gradually increased and the child variously placed on Olac® or Nutramigen® formulas. Despite these measures and despite various antispasmodics she continued to lose weight and on August 3 weighed 4 pounds, 14 ounces.

A transfusion was given. Cortisone, 25 milligrams daily, was administered and the formula increased to four ounces per feeding. Cereals were also added to the diet. In an attempt to discover the reason for continued weight loss a "sweat test" for mucoviscidosis was performed, but the results were inconclusive. Steroid therapy was gradually discontinued and again a new formula (Probana® 1:1) prescribed. Pancreatin was also added but discontinued when she began to regurgitate feedings. She gradually began to retain more feedings and the number of stools decreased. She began to gain weight slowly and at the time of this presentation (August 24, 1956) weighs 6 pounds and has a normal number of stools in 24 hours.

DISCUSSION

In addition to being a unique coexistence of abnormal gastro-intestinal findings, this case serves to bring to the reader's attention the thought provoking dictum of Gross[1] that "the finding of one atresia, above which the intestine is distended, should never be accepted as representing ALL of the pathologic abnormality present in the abdomen."

The presence of jejunal atresia alone occurred in only about 13 percent of Gross'[2] 140 cases of intestinal atresia while in 329 cases of congenital hypertrophic pyloric stenosis reviewed in this hospital[3], only 3 had other developmental defects, viz: two with umbilical hernias and one with a cleft palate. In neither series, however, was the combination found in our case noted. Baker and Sager[4] in their series report the presence of tumor in 74 percent of cases of pyloric stenosis, while Nelson[5] states that the tumor

can be felt in the majority of instances. Interestingly enough, as is noted above, no tumor was palpable in this case.

Certain data already noted in medical literature regarding pyloric stenosis are worth mentioning at this time. Pyloric stenosis has been known to a) occur in twins of the same family; b) occur in 6.9 per cent of children of parents who had pyloric stenosis, McKeown and McMahon[6]; c) be associated with the Bonnevie-Ullrich syndrome, Keay and Lewis[7]; d) be associated with adrenal insufficiency, Morec[8]; and e) be an etiologic factor in a case of jaundice, Martin[9]. With this case we feel that we have presented another interesting finding associated with congenital hypertrophic pyloric stenosis.

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CLINICAL PATHOLOGICAL CONFERENCE

Directed by E. Clarence Rice, M.D.*, and Grace H. Guin, M.D.†

Discussed by Francis J. Troendle, M.D.‡

This five year old white male child was admitted to Children's Hospital, having lapsed into a flaccid and unconscious state a few hours before admission. For two days he had been vomiting and had diarrhea, and during a period of two months he vomited from time to time. During the previous year he had failed to maintain his expected weight gain.

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The prenatal, neonatal and past histories were non-contributory. The father and six year old brother had had diarrhea during the six day period preceding the patient's admission.

Examination revealed a very pale white boy who was acutely ill and semi-comatose. Blood pressure was 85/30. Rhonchi were heard over both lung fields but these disappeared after vomiting. The physical examination was otherwise unrevealing.

On the day of admission the child received glucose intravenously and within 15 minutes after the injection the patient sat up and answered questions. Prior to the injection the boy appeared to be on the verge of a convulsion. His blood sugar was 87 mg. per 100 ml., and his spinal fluid was normal except for the absence of sugar. During this, the first hospital stay, the patient had a number of diarrheal stools. The neurological examination revealed inconstant findings such as jerky movements of the arms and legs, equivocal Babinski, dilated and equal pupils. On discharge the diagnosis was encephalitis, mild, type undetermined.

In six weeks the boy was readmitted in a coma of three hours' duration. Two weeks before this he began to sleep more than usual, the appetite waned and he vomited occasionally. He showed an increased desire for salt. There was no diarrhea. He had complained of abdominal pain. The day before hospitalization it was reported that he would clench his jaws, stiffen and flex his arms and his eyes would rotate upward. Physical examination on admission disclosed hypothermia of 96°F., coma and hypoactive knee jerks. The blood pressure was 80/40. The spinal fluid was clear and colorless, containing less than 1 cell per cmm., and 10 mg. sugar per 100 ml. The blood sugar at the same time was 48 mg. per 100 ml. As previously reported, he again roused from his stuporous state following the intravenous injection of 10 ml. of 10 percent glucose solution and appeared to be well oriented; however, he relapsed the following day but was restored to consciousness by the same treatment. Several black nevi, which had not been noted previously, were observed.

During this admission the fasting blood sugars varied between 37 and 100 mg. per 100 ml., and post-prandial sugars between 105 and 222 mg. A glucose tolerance test was normal. A galactose tolerance test was reported as showing an excretion of 2.4 gm. in five hours. The basal metabolic rate was reported as plus 20 percent. Prothrombin was reported as 80 percent of normal activity. The cephalin flocculation was 2 plus in 48 hours. Serum sodium was 116 mEq/L, chlorides ranging from normal to hyperchloremic levels. Wassermann and Kahn tests were negative. Blood culture was sterile. Hemoglobin remained at 9 gm. per 100 ml. with 3,300,000 erythrocytes per cmm. The leukocyte count varied between 7,800 and 17,500 per cmm. with 54 percent lymphocytes and 44 percent neutrophiles. An occa-

sional hyaline cast was found in the urine which otherwise was normal. Roentgen examination of the skull and abdomen disclosed nothing noteworthy. The tuberculin test was negative.

During this admission he received glucose intravenously and 1/6 molar sodium lactate. Over a period of three days he also received 2 ml. of adrenal cortical extract subcutaneously, and 1 gm. of sodium chloride three times daily. The patient's condition and behavior remained unchanged and he was discharged.

Four days later he was again hospitalized. The nevi seemed to be more numerous. Fasting blood sugars were again low, one blood chloride was below normal, and two others were normal. Electrocardiogram, x-rays of the chest and abdomen were reported negatively. The patient seemed to improve somewhat but on the thirteenth day of this hospitalization, and three months after the initial date of admission, he suddenly became comatose and died despite the intravenous administration of glucose.

DISCUSSION

Dr. Troendle:

This case is one of Addison's Disease, I believe. I would like to read portions of the protocol and mention diseases which might be considered at certain times during this child's history.

The patient was a five year old boy who was admitted to the hospital with a history of vomiting, diarrhea and unconsciousness. The cause of these findings could have been an enteric diarrhea; Shigellosis being possible or even a Salmonella infection. These signs could have been caused by any fulminating infection. A brain tumor or abscess and an encephalitis must also be considered, at this point. Diabetes Mellitus may manifest itself with these signs in children, although the typical associated findings of polydipsia, polyuria and polyphagia are usually present. Adrenal insufficiency may be manifested by vomiting and diarrhea, and rapid progression to coma.

The past history was non-contributory. Other members of the family had diarrhea about the time of onset of this patient's illness. This may be a red herring or an explanation of why this child became suddenly ill. He may have developed a specific enteritis which precipitated the presumed adrenal crisis.

On physical examination, no record of the child's temperature is given, and this fact is of interest to me. He was acutely ill and semi-comatose, with a significant hypotension 85/30 mm Hg. His type of breathing was unfortunately not recorded, because this might have allowed one to differentiate his condition from diabetic coma, where the breathing is rapid and of the Kussmaul type. No record of the child's pupils or fundi is given, which facts

might have helped in a differential diagnosis from a central nervous system lesion, like a brain tumor.

On the day of admission he was given intravenous glucose solution, and 15 minutes after the solution was given he sat up and responded well. This is obviously a very important point because, along with the later description of the cerebro-spinal fluid glucose being very low, this dramatic response to the administration of glucose has to be weighed very heavily. Certainly that tends to rule out a multitude of disorders which could have caused these general symptoms, such as diabetes with hyperglycemia, brain abscess, encephalitis, etc. Before the glucose was given, the child had been on the verge of convulsions. His blood sugar was 87 mg. per 100 ml. I presume that this determination was done by the Folin-Wu method, which this hospital has used for a number of years. Certainly I would call this reading within normal limits. There is no logical explanation, if this value is correct, of why he should be brought out of his coma by glucose. The spinal fluid was negative except for the absence of sugar and this finding is of tremendous importance. It is an easy test to do and I presume that the report is correct. There are only two things I know of that can cause an absence or marked decrease of sugar in the spinal fluid. One would be a specific bacterial infection of the meninges. The other condition which could cause a low spinal sugar is hypoglycemia.

The spinal fluid and blood sugars do not corroborate one another at first glance. However, it is well known that the spinal fluid glucose lags behind the blood glucose by approximately four hours. If these tests are correct, I assume that the blood sugar was very low a few hours ago and now has risen to its recorded value; the spinal fluid glucose is comparable to the blood glucose of four hours ago.

The blood sugar may have risen by the stimulation of hypoglycemia and the resultant adrenaline secretion, which may cause an elevation of blood glucose in two ways. One is a direct stimulation of the liver causing glycogenolysis; the other is by pituitary stimulation with production of ACTH. The latter antagonizes insulin in the hexokinase reaction and stimulates the adrenal cortex, producing further insulin antagonism and gluconeogenesis by adrenal hormone action.

The diagnosis at this point in the protocol must be one of hypoglycemia. The child was discharged with a diagnosis of "encephalitis, type undetermined." Admittedly, hind sight is better than foresight, but it is hard to figure how the diagnosis of encephalitis was arrived at.

Six weeks later the child was again admitted with the chief complaint of coma of three hours' duration. Two weeks before admission he began to complain of abdominal pain and had a poor appetite. There was vomiting but no diarrhea. The day before hospitalization he was reported to have

clenched his teeth, stiffened and flexed his arms and rotated his eyes upward. Typically these findings could go along with hypoglycemia. Physical examination at this admission showed for the first time a hypothermia and again hypotension. The spinal fluid contained 1 cell with a very low sugar content, 10 mg. per 100 ml. The blood sugar was 48 mg. per 100 ml.

A blood glucose of 50 mgm per 100 ml. is approximately the critical level at which most individuals begin to show hypoglycemic symptoms. After 10 ml. of 10 percent glucose were given intravenously, the child wakened suddenly and appeared well oriented; a beautiful proof of the response to glucose in the hypoglycemic child. A number of black nevi were noted at this time. Whenever I see black nevi, the first condition I think of is the Peutz-Jeghers syndrome (the association of pigmented nevi especially around the lips and buccal mucosa, and sometimes on the fingers with small bowel polyposis) but this condition obviously does not fit this case. In Addison's disease, the pigmentation is usually generalized and is accentuated around scars.

During the second hospital admission of this child, a blood sugar of 37 mg. per 100 ml. was recorded. This is very significantly low and along with the relative and absolute lymphocytosis, helps substantiate a diagnosis of adrenal insufficiency. The galactose tolerance test is normal as one would expect in adrenal insufficiency. The B.M.R. was recorded as plus 20 percent. This value does not fit my presumptive diagnosis and I am inclined to disregard it. Excitement could throw off a B.M.R. on the positive side very easily. A serum sodium was 116 mEq/L, a low value and one compatible with adrenal insufficiency. The high blood chloride value noted could be caused by intravenous saline administration; the low value fits the diagnosis I am entertaining much better. X-ray examination of the abdomen was negative. I have not seen calcification of the adrenal in Addison's disease in children; it is supposed to occur commonly in TB of the adrenal. The most common cause of adrenal destruction would be idiopathic rather than tuberculosis. This child had a negative tuberculin which helps rule out tuberculosis as an etiologic factor.

The treatment during this period consisted of intravenous administration of glucose, sodium lactate and a trifling amount of adrenal cortical extract presuming that this case is one of adrenal insufficiency. The child was discharged without improvement. Why he was discharged is a question I cannot answer.

Four days later the patient was re-admitted and expired on the thirteenth hospital day after becoming comatose. The pigmented spots were more numerous.

This Clinical Pathological Conference seems like a fairly classical case of Addison's disease. The child developed an infectious diarrhea which

caused loss of sodium and chloride and exhausted the already deficient adrenal cortex. His response to intravenous glucose rules out other causes of coma such as central nervous system damage or disease and leaves one with the diagnosis of hypoglycemia. Laboratory studies aid in pin-pointing the cause of the hypoglycemia to the adrenal cortex or the pituitary.

Another cause of hypoglycemia is ruled out readily after the lowered values for sodium and chloride are considered; this is idiopathic hypoglycemia that McQuarrie has described and treated so successfully. Liver damage and pancreatic beta cell hyperfunction are ruled out by the normal liver function tests and glucose tolerance test.

The laboratory values that fit the diagnosis of adrenal insufficiency are the low blood chloride, sodium and sugar, the relative and absolute lymphocytosis. The differential diagnosis, if one disregards the pigmentation, revolves around adrenal or pituitary insufficiency. A test of interest in differentiating these two conditions is the use of ACTH to stimulate ketosteroid excretion in the urine. Since a child this age excretes very little ketosteroid, I do not think this test would be rewarding. The use of ACTH to cause the lysis of circulating blood eosinophiles would be a helpful test in this differentiation, a positive result indicating the adrenal cortex is intact and pituitary function presumably affected.

The measurement of aldosterone excretion in the urine would be helpful. It is known that hypophysectomized patients excrete normal amounts of aldosterone, that is, the pituitary seems to have no effect on the adrenal in the regulation of aldosterone excretion. One finds normal urinary aldosterone in pituitary deficient cases with intact adrenals but an absence of aldosterone in cases of Addison's disease. Another differential point is the clinical finding of growth failure (dwarfism) in cases of pituitary deficiency due to lack of growth hormone.

Simmons' disease is said to cause pigmentation of the skin similar to that in Addison's disease but I have never heard of a case in a young child.

My diagnosis is adrenal insufficiency on the basis of Addison's disease with the probable destruction of all three layers of the adrenal cortex; the low blood sodium and chloride indicating zona glomerulosa damage, the low blood sugar indicating gluco-corticoid deficiency from zona fasciculata damage, the failure to gain weight suggesting a deficiency of androgens from zona reticularis damage.

Dr. Guin:

I want to thank Dr. Troendle for this thorough discussion. It is interesting that this is such a rare disease in children. This is the only case that we have had at Children's Hospital. As Dr. Troendle mentioned, there are two causes, either idiopathic or tuberculosis of the adrenal cortex. In

this case it was the idiopathic type; the right adrenal weighed 0.55 gm., and the left adrenal 0.5 mg., which was but 25 percent of their normal weights. On microscopic examination there was disintegration of most of the cells of all three layers of the cortex. The disintegration was characterized by fragmentation of the cytoplasm, the nuclei showing pyknotic alteration.

The pigmentation which is seen in this disease is pure melanin. It is deposited in the basal epithelial layers of the skin and it may precede by months the clinical onset of the disease. There have been several hypotheses to explain this pigmentation. Some have suggested that there is some pre-adrenalin material which is supposed to remain unoxidized. None of these hypotheses is satisfactory as they do not fit the clinical findings or the degree of involvement of the adrenal gland.

The course of Addison's disease is usually rather insidious but these patients tend to go into crises. Apparently this boy came into the hospital in crisis, and the gastrointestinal upset and the diarrhea were no doubt part of this picture.

I cannot understand the findings in the pituitary gland in this case. We do not have access to the pituitary slide, but the protocol states that there was an increase in the basophilic cells. The basophilic cells are increased in Cushing's disease, which is the opposite to this disease. They are ordinarily granular but in Cushing's disease the granularity is replaced by hyalinization which is called Crook's change. The significance of this change is not understood but it is certainly present in practically all cases of true Cushing's disease. The chromophobe cells are as a rule decreased in Addison's disease and may have given the impression of increase in basophiles.

Atrophy of the adrenal cortex is followed by hyperplasia of lymphoid tissue. We found at this autopsy that the lymph nodes were markedly enlarged. On microscopic section the lymph nodes were found to be hyperplastic. The opposite of this would be found in Cushing's disease. The spleen was 10 percent smaller than normal and the heart and liver were about normal in size. There were no other findings of importance.

Dr. Rice:

This is the only child who died of Addison's disease at this hospital that I can recall. I am under the impression that the brother of this boy developed adrenal insufficiency and was treated by Dr. Thorne in Boston. We have had a number of children admitted in coma with low blood sugar. One child whom I remember was admitted in coma having a blood sugar in the neighborhood of 60 mg. per 100 ml. (Folin-Wu). The correctness of the determination was doubted and two more determinations with the same

result were obtained. Finally, some one smelled the patient's breath and detected the odor of shoe polish. Apparently the hydrocarbons in the polish caused enough damage to the liver to lower the blood sugar to a hypoglycemic level. We have been interested in low glucose values in the spinal fluid where there was involvement of the meninges by the leukemic cells, making the differential diagnosis between bacterial meningitis and leukemic involvement of the meninges, a difficult one. Incidentally, I find it difficult to believe that 10 ml. of 10 percent glucose solution would bring this five year old child out of his coma.

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